Chapter 5

CHAPTER 5
Lateral parietal cortex in the generation of behavior: implications for apathy

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Abstract

A reduction in goal-directed behavior, or apathy, is an early prognostic marker of several neurological and psychiatric disorders. It has been attributed to deficits in neural circuits connecting the prefrontal cortex to the basal ganglia. A number of brain imaging studies have associated apathy symptoms in various disorders with widespread changes in the brain. Such variety in regional cerebral involvement is consistent with the suggestion of different subtypes of apathy. Although these studies include reports that apathy is associated with regions in the lateral parietal cortex (LPC), the role of this region in apathy is not appropriately recognized. From a cognitive neuroscience perspective, functions of the LPC are relevant for goal-directed behavior, and therefore dysfunction of this region may produce symptoms of apathy. Here, we review studies that report associations between parietal cortex dysfunction and apathy across disorders and investigate the putative cognitive processes in the LPC that may underlie such reduction of active behavior. Neural processes in this region provide an interface between basic features of sensorimotor transformation and core features of volition and action performance, thus enabling the transformation of internal goals to external actions. We infer that impairments in these processes may logically represent mechanisms underlying the association between the LPC and apathy. Considering the evidence, we propose that impairments in the lateral parietal cortex may lead to reduced goal-directed behavior and hence, suggest this region be included in neural models of apathy.

Chapter 5

1. Introduction

Performing complex behaviors is part and parcel of daily life. For example, getting from A to B in a city requires the dynamic interplay of several cognitive processes, ranging from long-term memory and attention to planning abilities and spatial navigation. Thus, to successfully accomplish such behaviors, a variety of cognitive functions that rely on multiple brain regions must work together in an integrated manner. Cognitive models that describe the generation of such complex behavior comprise of cognitive functions that begin with an internally or externally driven motivation to act, followed by planning, executing actions, evaluating outcomes with respect to selected goals, and if required, adapting subsequent actions (Brown and Pluck, 2000). Deficits in any cognitive function forming this sequence of processes may lead to impairments in the generation of complex behaviors. Such reduced behavior, which is clinically termed as apathy (Levy and Dubois, 2006; Robert et al., 2009), is observed across various neurological and psychiatric disorders. It is characterized by several observable symptoms, such as lack of initiative, loss of interest, or lack of effort in performing day to day tasks.

The neural substrates of apathy have been suggested to lie in circuits linking the prefrontal cortex to the basal ganglia (Brown and Pluck, 2000; Levy and Dubois, 2006; Marin, 1990; Starkstein, 2000; Stuss et al., 2000; van Reekum et al., 2005). The emphasis on frontostriatal circuits is easy to understand, as there is not only empirical evidence for their association in apathy (Kos et al., 2016; McIntosh et al., 2015; Pagonabarraga et al., 2015; Stella et al., 2014; Theleritis et al., 2014), but also known functions of these circuits correspond with deficits expressed in apathy (Hazy et al., 2007; Miller and Cohen, 2001). These functions include components of goal-directed behavior (GDB), mediated by the prefrontal cortex including storage and evaluation of stimulus information, evaluation of reward potential of specific actions, and generation of a plan of action (Hollerman et al., 2000). The basal ganglia, which by means of extensive dopaminergic circuitry, signals reward potential and acts as a final gateway in the production of motor movements (Goto and Grace, 2005). In short, these circuits appear to support cognitive functions necessary for GDB.

A critical reading of recent studies in different brain disorders, however, suggests that besides associations with the prefrontal cortex-basal ganglia regions, apathy is also associated with changes in the lateral parietal cortex (LPC) (Fig.1). This association, reported in diverse disorders, is of interest as the LPC does not find a place in current models of apathy (Bonelli and Cummings, 2007; Guimarães et al., 2008; Levy and Dubois, 2006; Starkstein and Leentjens, 2008; van Reekum et al., 2005). As a result, the reported associations between the LPC with apathy have been largely ignored and the cognitive basis of apathy symptoms due to impairments in the LPC have not been

explained. To address this issue, we review evidence associating apathy with impairments in the LPC, and evaluate the cognitive and neural mechanisms that contribute towards reduced behavior. We suggest that deficits in LPC-supported cognitive processes impair the control of goal-directed actions and the attribution of motor actions to one self, which may underlie the association of this brain region with reduced behavior. We further propose that the LPC be included in neural models of apathy. In the following sections, we review evidence supporting the involvement of the LPC in apathy, evaluate the cognitive processes involved, and present a new model for apathy emphasizing the role of the LPC.

2. Association between lateral parietal cortex and apathy across disorders

Symptoms of apathy are common in several brain disorders such as in neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), and fronto-temporal dementia (FTD), in stroke (or cerebrovascular accident), and in schizophrenia. In each of these disorders, apathy becomes increasingly prevalent and severe with disease progression (with the exception of stroke where symptoms may improve with functional recovery) (Dujardin et al., 2007; Geda et al., 2014; Landes et al., 2005; Starkstein et al., 2006). Given that apathy is a marker for worse prognosis, understanding its neural mechanisms can better characterize the primary disorder. In imaging studies across disorders, apathy is associated with deficits in multiple brain regions (Kos et al., 2016), with the most common region being the dorsal anterior cingulate cortex (ACC) (McIntosh et al., 2015; Pagonabarraga et al., 2015; Theleritis et al., 2014). However, as noted by Stella et al. (2014), apathy is also associated with other brain regions. Besides the dorsal ACC, apathy has been associated with deficits in sub-cortical regions, orbito-frontal cortex, and dorso-lateral prefrontal cortex [See Tekin and Cummings (2002) for a discussion on the accompanying cognitive deficits]. In addition to fronto-subcortical circuits, apathy has been linked been to the LPC in one third of the studies on neurodegenerative disorders and in about 14% of studies on psychiatric disorders (Kos et al., 2016). This association is present across imaging modalities including structural, metabolic, and functional imaging and is discussed below for the different clinical conditions. Figure 2 shows the location of regions (in the Montreal Neurological Institute atlas space) from studies associating apathy with the LPC.

2.1 Association of LPC with apathy in Alzheimer's disease

In AD, a progressive decline in cognitive functions is accompanied or in some cases, preceded by behavioral changes (Geda et al., 2008; Pietrzak et al., 2012). Apathy is the most common behavioral change in AD and when present in the prodromal stage, it increases the risk of disease progression (Peters et al., 2013; Rosenberg et al., 2013). Investigating the neural correlates of apathy, Ott and colleagues (1996) reported reduced cerebral perfusion in the right posterior temporal and parietal cortex in

association with apathy in AD patients. Moreover, global cognition (measured using Mini-Mental State Examination) was not associated with perfusion in these regions or with apathy, suggesting that symptoms of apathy are not captured by cognitive measures and also the associated brain regions may not necessarily overlap. In another study of seventy AD patients with apathy, similar findings were reported (Tanaka et al., 2004). Donepezil (a cholinesterase inhibitor) was found to have differing effects among the AD patients. In some patients (30%), symptoms of apathy, dysphoria and anxiety were reduced, whereas in ten percent of patients these symptoms worsened, and no effects were seen in the rest (60%). By contrasting the group with worsened symptoms to those in whom symptoms improved or remained unchanged, the authors found significant associations between apathy and reduced blood flow in the bilateral superior parietal lobule and the surrounding temporal cortices (Tanaka et al., 2004). Although this study included a small sample size, it provides evidence linking apathy to reduced blood flow in the parietal regions.

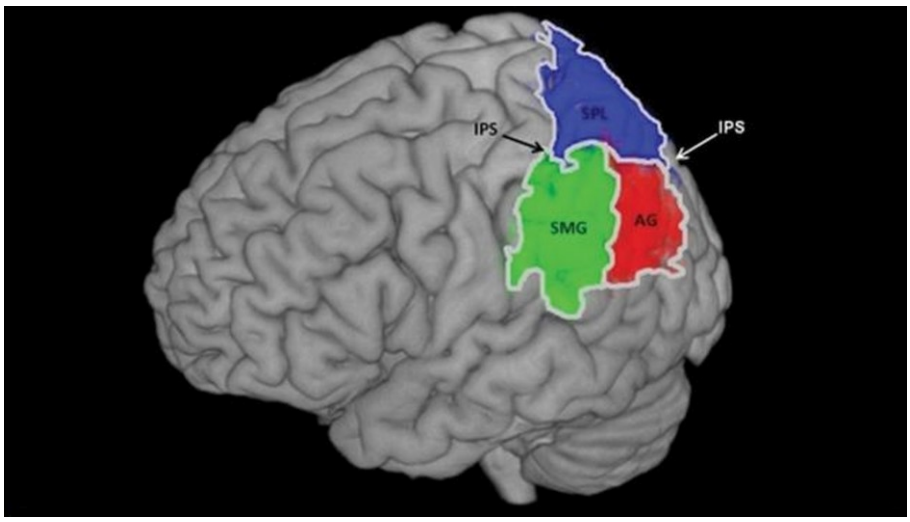
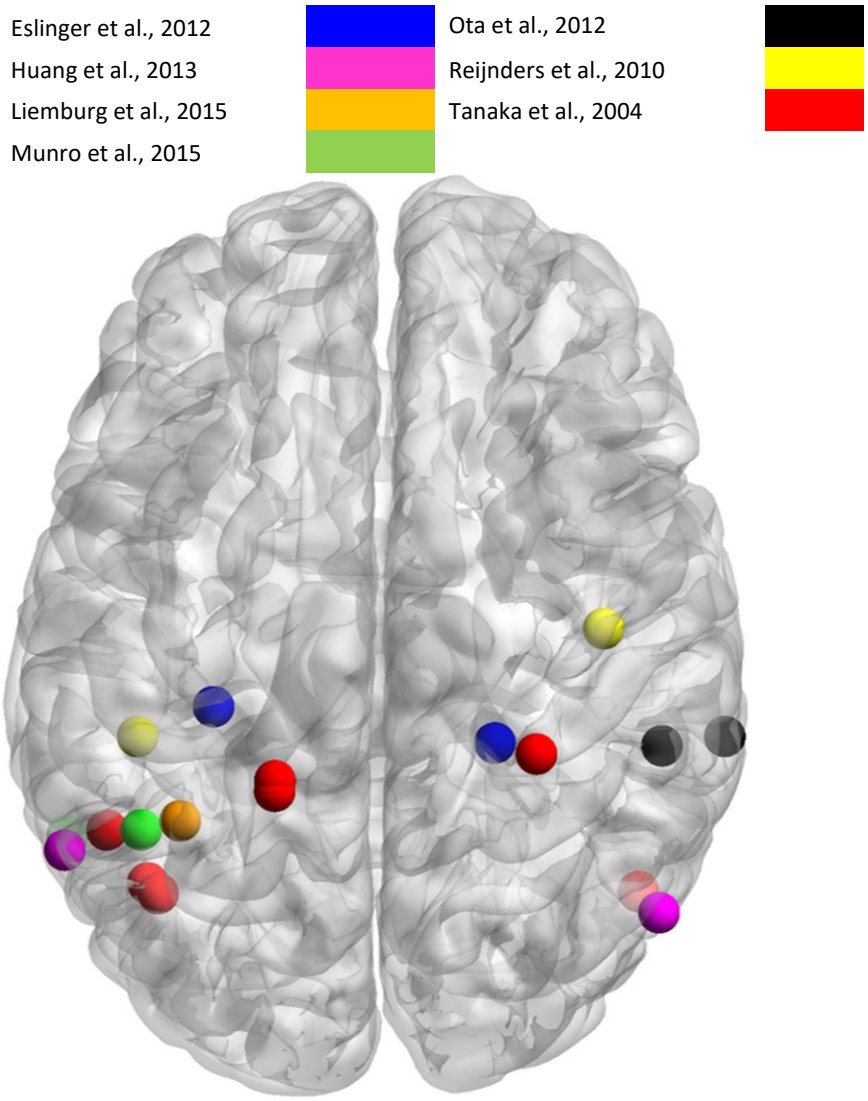


Fig. 1: Anatomical divisions of the lateral parietal cortex.
The superior parietal lobule (SPL) is shaded in blue. The inferior parietal lobule (IPL) comprises of the angular gyrus (AG) in red and supramarginal gyrus (SMG) in green. The SPL and IPL are separated by the intraparietal sulcus (IPS). In this review, the SPL and IPS are together labelled as the dorsal lateral parietal cortex (LPC), and the SMG and AG are together labeled as the ventral LPC. The term ventral LPC is used interchangeably with the IPL. (Adapted from Humphreys and Lambon Ralph, 2015)

Fig. 2: Empirical associations between lateral parietal cortex and apathy
Peak coordinates from studies that reported an association between apathy and the lateral parietal cortex are projected on to a brain template. The size of the regions of interest are arbitrary and are not scaled to the reported cluster sizes (in some studies).



In addition to reduced blood flow, apathy was found to be associated with reduced cortical thickness of the right superior and inferior temporal cortex in patients with mild cognitive impairment (MCI) (Guercio et al., 2015), as well as predictive of increased severity of apathy symptoms in MCI and AD patients (Donovan et al., 2014). Furthermore, changes in white matter in the LPC have also been associated with apathy in AD. More specifically, damage in the white matter of the right parietal lobe in the form of hyperintense lesions, indicative of vascular pathology, was found to be increased in probable AD patients with apathy and comorbid depression (Starkstein et al., 2009). Using diffusion imaging to characterize nerve tracts in twenty one AD patients, Ota and colleagues (2012) found that apathy was associated with reduced fractional anisotropy, indicative of damage to nerve fibers, in the bilateral parietal cortices. Measures of diffusion such as fractional anisotropy can be used to delineate major white matter tracts. In one such analysis, the right superior longitudinal fasciculus, which carries nerve fibers between the frontal and parietal cortex, was shown to have reduced integrity in AD patients with apathy (Hahn et al., 2013). Notably, this study assessed apathy symptoms using the Apathy Inventory (AI), which quantifies the severity of apathy as opposed to the common practice of assessing the presence/absence of apathy. The findings of impaired structural connectivity are supported by a recent study where affective symptoms, particularly apathy, were associated with reduced functional connectivity (correlation between time-courses of activity in brain regions) in the fronto-parietal control network (FPCN) in patients with MCI (Munro et al., 2015). Thus, a number of studies in AD patients have reported apathy to be associated with deficits in the lateral parietal and temporal regions, particularly in the right hemisphere.

2.2 Association of LPC with apathy in Parkinson's disease

In PD, atrophy of dopaminergic neurons in the brainstem is accompanied by characteristic motor symptoms of tremors and rigidity. In addition to motor symptoms, neuropsychiatric features are also common in PD (Chaudhuri et al., 2006). Symptoms of apathy are diagnosed in a quarter to one-third of patients in the early stages of the disease, and with progressive worsening, this proportion increases (Pagonabarraga et al., 2015). Like in AD, apathy in PD is also associated with changes in multiple brain regions with prefrontal-subcortical circuits being affected most often (Pagonabarraga et al., 2015). However, apathy has also been associated with changes in the LPC. In early PD patients, Reijnders et al. (2010) found reduced grey matter density in a number of regions including the bilateral inferior parietal lobes to be associated with apathy. In this study, apathy was characterized with multiple assessment tools and the apathy score derived with each tool was found to be associated with nearly identical brain regions (Reijnders et al., 2010). In another study investigating metabolic changes in early stages of PD, apathy was found to be associated with reduced glucose metabolism in the right inferior parietal lobule (Huang et al., 2013). In addition to using the Apathy Evaluation

Scale (AES) to assess apathy symptoms, which quantifies apathy (similar to the AI), this study also found reduced motor functions to be associated with reduced metabolism in the inferior parietal lobule. Results from functional imaging acquired under resting conditions also converge on the inferior parietal lobule as the locus in the LPC that is associated with apathy in PD (Skidmore et al., 2011). Together, these findings suggest that dysfunction in the inferior parietal lobule of the LPC plays a role in the development of apathy and that reduced motor function may mediate this association.

2.3 Association of LPC with apathy in fronto-temporal dementia

Apathy is also a common symptom of FTD, which is characterized by atrophic changes in the frontal and temporal lobes of the brain. Symptomatically, behavioral disturbances are prominent in FTD, which occur either in the form of increased behavioral activity such as loss of inhibition, inappropriate behavior, and repetitive actions, or manifest themselves in the form of reduced self-initiated behavior (i.e., apathy) (Mendez et al., 2008). Both clinical presentations of FTD are correlated with atrophic changes in the frontal lobes. However, similar to AD and PD, apathy in FTD has also been associated with the LPC. In a moderately sized sample of FTD patients, the severity of apathy, as measured by the apathy sub-scale of the frontal systems behavior scale, was associated with reduced gray matter density in the lateral frontal cortex as well as the right inferior parietal lobule (Zamboni et al., 2008). Similar results were also found in a smaller sample of patients with the behavioral variant of FTD where the apathy score was based on caregivers' report and was associated with reduced gray matter density in the broader temporo-parietal region (Eslinger et al., 2012). Compared to late-onset FTD patients with disinhibition and healthy control subjects, FTD patients with apathy showed atrophy and hypometabolism in the lateral frontal cortex and the inferior parietal lobule (Morbelli et al., 2016).

2.4 Association of LPC with apathy in stroke and schizophrenia

The LPC is also associated with apathy in post-stroke syndromes. In a three-year follow-up of a single subject who developed apathy following a stroke, functional connectivity of the inferior parietal lobule along with that of the ACC was found to be altered (Siegel et al., 2014). The normal positively correlated activity between the inferior parietal lobule and medial frontal brain regions was reversed and normal positive correlation with other brain areas was reduced. In this single case study, apathy was associated with changes in multiple cortical and subcortical areas. That apathy is associated with multiple regions of the brain including the LPC is also borne out by a study in a large sample of stroke patients (Yang et al., 2015) where structural connectivity (measured by diffusion imaging) was reduced within a network of regions that involved the LPC. Among studies using task-based functional imaging, Liemburg et al., (2015) found that brain activation was reduced in the inferior parietal lobule while

performing the Tower of London task in association with greater apathy in schizophrenia patients.

2.5. Summary of findings and their relation to neural models of apathy

In the above-mentioned studies, symptoms of apathy in brain disorders with varying etiologies were associated with altered structure, function and metabolic activity in the LPC. Although, associations of apathy with the LPC were reported in these studies, the findings were not extensively discussed or considered to be of significance. A likely reason for this may be that in a majority of these studies, apathy was associated with multiple brain regions including the dorsal ACC, medial prefrontal cortex or basal ganglia. The consistent association of apathy with these regions lends support to neurocognitive models where deficits in the prefrontal cortex – basal ganglia circuits are proposed to be the neural basis of apathy (Brown and Pluck, 2000; Guimarães et al., 2008; Levy and Dubois, 2006; van Reekum et al., 2005). These models also describe the cognitive mechanisms supporting GDB where apathy may result either due to an inability to evaluate the reward potential of an action (behavioral apathy, consistent with deficits in the medial prefrontal cortex), or deficits in executive functions (cognitive apathy, consistent with deficits in the lateral prefrontal cortex) or deficits in spontaneous activity (auto-activation deficit, consistent with deficits in the basal ganglia) (Brown and Pluck, 2000; Levy and Dubois, 2006). However, current models of apathy do not explain the empirical associations between the LPC and symptoms of apathy.

In the next section we focus on the behavioral deficits that result from isolated lesions of the LPC and may underlie symptoms of apathy. We also review the relevant literature from a cognitive neuroscience perspective to understand the basic cognitive mechanisms that are supported by the LPC. Based on these studies, we build a case for the cognitive basis for symptoms of apathy resulting from deficits in the LPC.

3. Evidence from lesion studies: the role of the LPC in generating behavior

Successful goal-directed behavior relies on a number of cognitive processes (Brown and Pluck, 2000), which in turn are supported by distributed brain networks. Key regions in these networks, especially in the association cortices, may be recruited by multiple cognitive processes (Culham and Kanwisher, 2001; Duncan and Owen, 2000; Ebitz and Hayden, 2016). The LPC, in particular, is activated during diverse cognitive processes such as attention, working memory, spatial cognition, and social cognition (Cabeza et al., 2012; Humphreys and Lambon Ralph, 2015). As a result of supporting diverse cognitive processes, damage to the LPC results in complex syndromes with varying symptoms, some of which may affect the motor aspects of behavior generation.

3.1 Apraxia and neglect: deficits in the cognitive control of actions

Classically, lesions in the parietal lobe are associated with apraxia where patients are unable to perform skilled motor movements, in the absence of sensory, motor, or muscular disorders (Geschwind and Damasio, 1985). Among the subtypes of apraxia, the ideational and ideo-motor forms are particularly relevant to GDB. Both subtypes involve transforming abstract concepts of an action and precise execution of complex motor movements. While the definition and neural substrates of each subtype are debated (Buxbaum et al., 2014), ideational apraxia refers to difficulty in generating complex movements when using an object, (De Renzi and Lucchelli, 1988) and ideo-motor apraxia refers to difficulties in performing an imagined movement on command, i.e., pantomiming (De Renzi et al., 1980). Various models have been proposed to explain the observed deficits in ideational apraxia including loss of knowledge of object usage (De Renzi and Lucchelli, 1988), disordering of action sequence (Poeck and Lehmkuhl, 1980), and incorrect activation of relevant schemas and suppression of irrelevant schemas at appropriate times (Norman and Shallice, 1986). These models point towards deficits in specific stored action plans in apraxia.

Ideomotor apraxia, on the other hand, is considered more sensitive to motor control since the absence of a tool or object deprives sensory input, which likely supports the execution of actions (Goldenberg et al., 2004). This sensitivity has a direct bearing on GDB since it implies that pantomiming requires intentionally activating a specific action sequence towards an imagined goal while constraining other stored schemas resulting in accurate and meaningful motor movements. Models of ideomotor apraxia (Buxbaum et al., 2000; Cubelli et al., 2000; Gonzalez Rothi et al., 1991) broadly involve conversion of action semantics and gesture patterns to motor output. In particular, Buxbaum et al., (2000) emphasize upon the dynamic regulation of intrinsic body schema in the production of gestures, based on a case-study of apraxia. In this model, gesturing deficits arise not due to deficits in stored action schemas but due to deficits in the interaction between the stored schemas and internal coding of body positions. The production of an intentioned action fails due to an inability to provide a continually updated body schema. In case of actual tool use, deficient interaction between the action schema and body schema is compensated by sensory and visual feedback.

Another view of ideomotor apraxia suggests that deficits arise due to difficulties in selecting the appropriate action schema, rather than deficits in or between action and body schemas (Bekkering et al., 2005). This view regards imitation as a goal to be achieved by selecting the appropriate action schema. A recent voxel-based lesion-symptom mapping study in a large number of patients provided a neuroanatomical basis for the deficits of ideomotor apraxia (Buxbaum et al., 2014). In this study, pantomiming was more strongly associated with lesions in the posterior temporal lobe, while imitation of meaningless gestures was more strongly associated with lesions in the parietal lobe.

This result suggests that motor control of action is achieved through multiple brain regions in the postero-lateral regions of the brain (Buxbaum et al., 2014). The findings can help understand the impairment of externally-directed goal-directed actions: conversion of verbal cues (evoking semantic knowledge) to action is supported by the posterior part of the temporal lobe, whereas imitation, which implies converting a visual cue to actions is supported by the parietal lobe.

Similar to apraxia, neglect is also classically associated with damage to the parietal (Azouvi et al., 2002; Hillis et al., 2005; Mort et al., 2003; Vallar and Perani, 1986) and the superior temporal lobule (Karnath et al., 2004; Ringman et al., 2004), as a result of which patients fail to attend to stimuli present on the contralesional side, in the absence of sensory and motor deficits (Mesulam, 1999; Vallar, 1998). This complex condition provides insight into another function of the lateral parietal and posterior temporal cortices – encoding a spatial map. Studies show that an egocentric and an allocentric map are encoded by the LPC and the temporal lobe, respectively (Hillis et al., 2005; Ota et al., 2001; Verdon et al., 2010). However, the debate on the neural distinction between the types of maps is not settled (McGlinchey-Berroth et al., 1996; Molenberghs and Sale, 2011; Rorden et al., 2012).

With respect to its functional basis, various theories have been put forth. One theory suggests neglect occurs due to deficits in the LPC in selecting the objects to be perceived (Bartolomeo and Chokron, 2002), while another theory suggests that the deficit lies in the direction and maintenance of attention (Corbetta and Shulman, 2002). A third theory asserts that it is not perception but spatial working memory that is affected in neglect (Pisella and Mattingley, 2004; Vuilleumier et al., 2007). Another theory suggests that motor control involved in initiation of arm (or eye) movement, and not cognitive functions, which is deficient in neglect (Kubanek et al., 2015; Mattingley et al., 1998). With respect to GDB, studies in neglect link spatial and body maps to the postero-lateral regions of the cortex, and indicate the various cognitive and motor control functions supported by this region.

Considering apraxia and neglect together, we can conclude that normal LPC function is necessary for controlling complex actions with reference to the environment. Furthermore, detailed analysis of symptoms and associated lesion sites in these disorders indicate that parietal dominant lesions produce symptoms indicative of deficient egocentric spatial functions while lesions in the posterior temporal region produce symptoms that indicate deficient processing of externally generated cues such as verbal commands and object features.

3.2. Insights into LPC function from distinct syndromes

Besides the common syndromes consequent to LPC lesions, circumscribed lesions in this area produce rare syndromes that can provide insight into LPC mechanisms contributing to reduced behavior. In these syndromes, complex and seemingly unrelated symptoms occur together, which suggest that focal regions within the LPC also support multiple functions. For example, in Gerstmann's syndrome, lesions in the inferior parietal lobule result in acalculia, finger agnosia, agraphia and left-right confusion (Gerstmann, 1930). Lesions in the angular gyrus (Mayer et al., 1999; Morris et al., 1984; Roux et al., 2003) may be responsible for producing a disordered mental body schema (Gerstmann, 1930).

In some instances, focal lesions in the LPC, typically subsequent to a stroke, result in the alien hand syndrome. Patients with this syndrome present with complex goal-directed hand movements that occur without volition or intention of the patient (Assal et al., 2007; Doody and Jankovic, 1992). As a result, the hand is perceived to out of voluntary control, which implies loss of sense of ownership and gives the disorder its name. In patients with LPC lesions, the movements observed are less complex but produce a stronger sense of loss of ownership, and accompanied by other symptoms like neglect and disordered body schema (Hassan and Josephs, 2016). In the context of self-generated behavior, the alien hand syndrome suggests that the LPC contributes to the perception of motor movements as being intentional by integrating neural signals of motor preparation, initiation or execution with visual and proprioceptive cues of movement. Deficient integration of these processes may contribute to the loss of agency, particularly when such deficiency includes impaired matching of predicted sensory consequences of movement and the actual sensory feedback (de Jong, 2011).Such loss of agency has been suggested to also play a general role in apraxia (Pazzaglia and Galli, 2014).

The loss of complexity in movements in the parietal variant of alien hand syndrome indicate that in addition to intentional movements, the LPC is also involved in fine control of the intended movement. Indeed, studies in patients and healthy subjects have shown that the posterior parietal cortex dynamically controls adjustments in hand movements even after the movement has been initiated (Mutha et al., 2014; Pisella et al., 2000; Vingerhoets, 2014). This is illustrated in a patient with bilateral lesions in the posterior parietal cortex who was able to grasp an object when its position was maintained at one location during a trial but failed to do so when the object was moved during the trial (Gréa et al., 2002; Rossetti et al., 2005).

Based on the evidence from lesion studies, LPC functions include the integration of sensory cues with precise execution of actions. Since brain lesions are expansive in nature, the affected region(s) cross anatomical boundaries and are not uniform across patients. As a result, accurate localization of affected functional

processes is difficult. From the functional deficits in patients with lesions, two broad domains of the LPC can be delineated. First, the dorsal region of the LPC consisting of the superior parietal lobule and intraparietal sulcus (Fig. 1) supports visuo-spatial attention and control of fine motor movements. Second, the ventral region of the LPC (inferior parietal lobule) consisting of the angular gyrus and supramarginal gyrus supports generation of intentional actions and attribution of motor movements to oneself. The adjoining posterior temporal cortex integrates semantic cues with intentional movements. This functional segregation coincides with findings from cognitive neuroscience studies where the dorsal LPC is considered to support visuospatial parameters coding external spaces and movement direction, and the ventral LPC contributing to proprioceptive processing, which facilitates maintenance of one's body scheme and serves efficient motor control (Beudel et al., 2011; de Jong et al., 2001; Hinkley et al., 2007). Together, the two broad divisions of the LPC support the cognitive control of motor behavior.

4. Framework of Goal-Directed Behavior and role of the LPC

In Section 1, we introduced GDB as the key cognitive framework that is disrupted in apathy. In Section 3, we described the behavioral deficits resulting from lesions of the LPC. Taking account of the complex syndromes that follow these lesions, it is clear that the LPC supports a variety of functions. This multifaceted nature is necessary for the higher-order integration of information from multiple sensory sources. From the preceding section, we concluded that deficits in spatial control of movement and body schema form two pathways that may reduce the generation of behavior. To further describe the basic mechanisms that underlie such deficits, we delve into the cognitive processes associated with the LPC in healthy individuals in order to draw linkages between the detailed framework of GDB and the relevant but broad functions that were inferred from lesion studies of the LPC.

Models of GDB provide a framework of cognitive elements that are needed for successfully reaching a predetermined end point (Brown and Pluck, 2000; Verschure et al., 2014). A key initial step in such a framework is the formation of an intent to act, driven by external or internal cues. A second component includes planning, which can be broken down into the representation of a goal, determining a sequence of actions aimed towards the goal, and selection and timing of actions during execution. The final component entails the initiation and execution of actions. In addition, a set of supervisory processes is essential for ensuring that actions are directed towards the goal, and if not, to incorporate necessary adaptations into the action sequence. A function that is implicit for any action and clearly associated with GDB is sense-of-agency, which is the subjective knowledge that an action is performed out of one's volition. Verschure and colleagues (2014) describe these processes in terms of 'what', 'why', 'when',

'where', and 'how'. In other words, the 'why' component posits the goal and the reason for its choice; the 'what' component represents the broad plan of action; the 'when' and 'where' components reflect the spatiotemporal aspects of the actions; the 'how' component describes the detailed motor sequences to be performed (Verschure et al., 2014). Notably, the authors distinguish between internal and external cues of GDB, with the former relying on longer time-scales, driven by memory and internal states.

4.1. Roles of the dorsal and ventral LPC in performance of intentional actions

Cognitive neuroscience studies provide a rich body of evidence for assigning key roles regarding individual functions in the framework of GDB to specific brain regions. Here, we focus on the GDB-related cognitive functions associated with the LPC.

4.1.1. Attentional control, action planning, and regulation of motor movements

The dorsal part of the LPC, comprising of the superior parietal lobule and intraparietal sulcus, supports neural representations necessary for top-down attentional control, spatial representation, and execution of complex motor movements (Andersen and Cui, 2009; Corbetta and Shulman, 2002; Gallivan et al., 2011). For performing a series of actions, these functions must be integrated (Humphreys and Lambon Ralph, 2015). Thus, a cross-modal functional integration may occur in the following form - mental simulations are performed of planned actions, an optimum action plan is selected and execution of the action sequence is initiated. The visual and somatosensory feedback from actions are evaluated and the motor plan is continuously updated to maintain a trajectory towards the goal (Battaglia-Mayer et al., 2014).

The dorsal LPC, especially the superior parietal lobule is activated during top-down tasks (Corbetta et al., 1995). This activation is paired to pre-formed responses such as when searching for specific visual cues presented among a set of distractors (Corbetta and Shulman, 2002). Top-down attention is also necessary for spatial working memory, which maintains a representation of salient cues for a short duration after the cue is changed or removed (Awh and Jonides, 2001). Activity in the dorsal LPC is also implicated in selecting motor actions, updating of the plan of action and in tracking outcomes of the action (Caminiti et al., 2010; Desmurget et al., 1999). This region is also active during sequential movements, whether self-performed, imagined/planned, or performed by others, which are achieved through sensorimotor integration (Cui, 2014).

Within the dorsal LPC, the superior parietal lobule is more strongly linked to spatial orientation, planning, and maintenance of attention on a task whereas activity along the intraparietal sulcus is associated with effectors such as in the dynamic adjustment of eye and hand movements during a task (Gallivan et al., 2011; Glover,

2004; Tunik et al., 2005). The former is suggested to rely on multiple sensory and cognitive inputs while the latter guides actions towards the goal (Glover, 2004).

Besides externally-directed planning, action performance also involves (internal) preparation of the body for executing the requisite motor plan. Pertaining to execution of actions, Beudel and de Jong (2009) contrasted two visuo-motor tasks and found that the superior parietal lobule was activated only when an instructed finger was to be guided to a fixed button as compared to when an instructed button was to be pressed with a fixed finger. After the initiation of planned actions, the intraparietal sulcus regulates spatial and temporal adjustments in movements to reach a target (Tunik et al., 2005). To support dynamic adjustments to movements, the intraparietal sulcus is suggested to store goals of an action, to which the executed action and its outcomes are compared, and in case of a mismatch, corrective movements are initiated (Tunik et al., 2007).

This inferential view is supported by evidence that the intraparietal sulcus is active in selection of a movement. When presented with alternative response choices encoded in the lateral frontal brain regions, the intraparietal sulcus signaled the selection of the appropriate choice (Muhle-Karbe et al., 2014). Activity in this region was disrupted by transcranial magnetic stimulation in close temporal proximity to selection of the appropriate response, which resulted in more errors as compared to control subjects. Furthermore, this study aimed to distinguish the role of the inferior frontal gyrus, which was found to be associated with updating of task goals, and the intraparietal sulcus, which was associated with responses to the task (Muhle-Karbe et al., 2014). Similarly, the initiation of adjustments to an action were disrupted by TMS to the intraparietal sulcus but had no effect if stimulation was applied after adjustments were already initiated (Glover et al., 2005). An alternative view suggests that the superior parietal lobule and intraparietal sulcus both store representations of motor plans, but the latter is active earlier than the former (Verhagen et al., 2013).

Taken together, the dorsal LPC appears to contribute to motor cognition by dynamically regulating goal-directed action: movements are planned by selecting the effector (Beudel and de Jong, 2009), the appropriate action is chosen from multiple responses encoded in the lateral prefrontal cortex (Muhle-Karbe et al., 2014), and then spatial and temporal control over motor movements is maintained so that they remain oriented towards intended goals (Glover et al., 2005; Tunik et al., 2007; Verhagen et al., 2013). Thus, the superior parietal lobule and the intraparietal sulcus together translate abstract goals represented in the frontal lobes to specific motor plans and regulate their execution (Muhle-Karbe et al., 2014).

4.1.2. Volition – intention and sense of agency

Besides attentional control, planning, and regulation of motor movements, performing goal-directed actions requires volition or what is perceived as the will to act. The act of choosing such actions needs to be distinguished from habitual movement, which can be complex but not necessarily resulting from conscious intent. In apathy, assessing whether patients lack initiative in performing activities directly relates to the concept of volition. Also termed free will, volition encompasses the experience of temporally distinct concepts of an intention to act, selection of an appropriate action, and attributing the outcomes to self-initiated actions. Studies over two decades have extensively investigated the neural basis of volition and evidence converges towards the inferior parietal lobule being key to volitional processes in the brain (Haggard, 2008).

The intention to act can be detected prior to motor movements being initiated. First reported as fluctuations in brain activity on electroencephalographic recordings, the 'bereitschaftspotential' or readiness potential has been interpreted as neural activity that reflects motor preparation preceding movement or planning of an action (Kornhuber and Deecke, 1965). Such activity preceding an action can be recorded from different parts of the brain such as the pre-supplementary motor area, basal ganglia and the LPC (Colebatch, 2007). Here, it is important to distinguish the effects of each region on motor movements in order to determine their roles in generating voluntary actions. The input from the basal ganglia to the pre-supplementary motor area plays a key role in activating effectors whereas activity in the dorsal LPC regulates movements as elaborated in the preceding section. The ventral LPC or inferior parietal lobule appears to generate the intention to perform an action (Sirigu et al., 2004). Patients with lesions in this region were aware of the performed movement but unable to recall if they were aware of the intention to move. The inability to experience intentions can lead to misattribution of the agent of the action. Apraxic patients with parietal lobe damage show reduced ability to distinguish movements of self from those of others (Sirigu et al., 1999). The discrimination between self and other is also affected in non-motor functions. Schizophrenia patients with auditory-verbal hallucinations (misattributing the agent of thoughts) show altered morphology of the inferior parietal lobule (Plaze et al., 2015). Thus, intention and sense of agency are coupled and typically integrated during voluntary actions. This coupling is particularly made evident by the notion that intention implicitly includes prediction of action effects.

Brain stimulation studies have provided evidence for the contribution of various regions to motor movements and volition. Stimulating the pre-supplementary motor area produces the inclination or even urge to move a body part, such as the hand or lips depending on the location of stimulation. As the strength of the stimulation is increased, factual movement of that body part occurs (Desmurget et al., 2009; Fried et al., 1991). A similar 'urge to act' is also produced on stimulating the inferior parietal

lobule. A crucial difference between the two stimulation sites is that on supra-threshold stimulation of the inferior parietal lobule, subjects sensed movements in the said body part despite absence of any such movement (Desmurget et al., 2009). In contrast, stimulation of the mesial pre-central area, a region close to motor areas, elicited compulsive feelings to perform an action. Importantly, the sensation of impending movement was not perceived as self-willed (Desmurget et al., 2009). Contrasting these outcomes, the inferior parietal lobule appears to be crucial to experiencing intention and perceiving (even when movement has not occurred), while the pre-supplementary motor area activates movement but does not contribute to perceiving it as self-generated. This study is in line with previous evidence showing that patients with damage to the angular gyrus in the inferior parietal lobule report a delay in experiencing motor movements until just before (~50 ms) an action is performed, as compared to healthy subjects (~250 ms) (Sirigu et al., 2004). Thus, the inferior parietal lobule plays a key role in receiving feedback of motor movements and in the perception of the inputs as self-generated.

The viewpoint mentioned above is strengthened by results from Haggard and Cole (2007). The authors reported that the inferior parietal lobule is highly active when subjects recognize that observed outcomes were due to their own actions. Conversely, lower activity was found in this region when subjects perceived a dissonance between their actions and outcomes. A recent study suggests that sense of agency may also be prospective, i.e., whether an action is attributed to oneself may be experienced before performing the action (Chambon et al., 2015). To test this hypothesis, neural activity in the inferior parietal lobule was disrupted using transcranial magnetic stimulation, which resulted in reduced perception of self-control on subsequent actions. In other words, the inferior parietal lobule may also play a role in movement preparation, which may contribute to perceiving actions as intentional. This view is supported by the study of Verhagen and colleagues (2013) who found that movement planning occurs in the dorsal as well as ventral LPC in parallel and that the ventral LPC can compensate for perturbations in the dorsal LPC.

In sum, the ventral LPC contributes to movement planning and attributing actions to oneself or in other words, intention and sense of agency are represented in the same brain region. Together, these results suggest that in motor cognition, the ventral LPC plays a crucial role as an interface where motor actions are associated with self-related processes and vice-versa.

5. Integration of functions supporting self-generated behavior

Generating goal-directed actions in response to internal and external stimuli is a fundamental function of the brain, for which information from internal and external

stimuli must be integrated. The LPC, especially the inferior parietal lobule, appears to plays a key role in this process as evidenced in the sections above. Besides the cognitive aspects of action generation, the LPC is activated by other cognitive processes such as episodic memory (Cabeza et al., 2012). The mechanism that enables the overlap of various cognitive processes within the LPC (Humphreys and Lambon Ralph, 2015) may be that this region receives signals from multiple brain networks (Braga et al., 2013) making it a candidate region for multi-modal integration essential for GDB.

Functional brain networks comprise distant regions that show spontaneous and coordinated activity (Fox et al., 2005). This functional organization of the brain is based on a framework of structural connections and is present in states of rest as well as sleep (Greicius et al., 2009). The default mode network (DMN) comprises of midline structures in the anterior and posterior cortical regions, and the inferior parietal lobule in the LPC (Raichle et al., 2001). Also termed the task negative network, the DMN is more active when individuals are not engaged in any task or are asked to not think of anything in particular. When performing cognitively demanding tasks that require problem solving and working memory, the DMN typically shows reduced activity while areas in the lateral frontal cortex and parietal cortex are activated (Fox et al., 2005). The task positive regions with anti-correlated activity with the DMN are segregated into the FPCN consisting of regions in the rostrolateral prefrontal cortex and the inferior parietal lobule and active when performing executive functions (Vincent et al., 2008), and the dorsal attention network comprising of the superior pre-central gyrus and the superior parietal lobule, which are active during tasks requiring sustained attention (Fox et al., 2006). The specialized cognitive processing in individual networks provides a basis for a neurocognitive framework for GDB.

5.1. Functional activity in the LPC and goal-directed behavior

When performing cognitive tasks, brain networks function as segregated but not isolated systems and cognitive performance is supported by between-network connectivity (Cole et al., 2014; Krienen et al., 2014). Such an interactive functional network may be especially crucial for goal-directed cognitive activity. Spreng et al. (2010) investigated the activity of the DMN and the FPCN under two conditions requiring autobiographical planning based on personal goals related to debt and employment, and an externally-directed visuo-spatial planning task (the tower of London test). The FPCN was found to interact with the DMN and dorsal attention networks in self-related and externally-directed conditions, respectively. The authors concluded that the FPCN ‘may flexibly couple with the default and dorsal attentional networks’ and act as ‘a cortical mediator linking the networks in support of goal-directed cognitive processes’. Thus, these results support the view that internally- and externally-directed cognition relies on

interactions between the FPCN and DMN, as well as FPCN and dorsal attention network, respectively.

The inferior parietal lobule is activated in response to a variety of tasks and its further functional subdivision into regions that participate in the DMN and FPCN is not clearly demarcated (Humphreys and Lambon Ralph, 2015). In addition, this region is uniquely represented in two large networks in the brain (DMN and FPCN), and interacts with the superior parietal lobule and intraparietal sulcus of the dorsal attention network (Vincent et al., 2008; Spreng et al., 2010). The supramarginal gyrus in the inferior parietal lobule shows overlapping activity with the DMN, dorsal attention network and salience network (comprising of the dorsal ACC and insula) (Braga et al., 2013). That the inferior parietal lobule shows functional connectivity with the salience network in addition to the DMN, FPCN, and dorsal attention network may be pertinent to the generation of behavior as the dorsal ACC is the most commonly affected region in patients with apathy (Kos et al., 2016; Stella et al., 2014).

5.1.1. Dissociation between external and internal choices

The role of the LPC and the dorsal ACC in GDB is illustrated in the study by Beudel and de Jong (2009). When participants were asked to select one of four buttons representing a free external choice, the dorsal ACC was activated together with the ventral LPC, whereas only the ventral LPC was activated when subjects were asked to choose a finger to press a fixed button. This finding is consistent with the results in a similar study using a finger-tapping task, where the LPC was activated during conditions where a choice was to be made and the dorsal ACC (and supplementary motor cortex) was found to be active during action selection (Zhang et al., 2012). Not only is the distinction in brain regions present when performing a task but also when planning for externally- and internally-directed tasks (Ariani et al., 2015).These results suggest that the dorsal ACC and LPC contribute to different aspects of the decision-making process in behavior generation. While the dorsal ACC plays a role in external choices, the ventral LPC plays a role in making internal as well as external choices. Thus, externally- and internally-directed motor cognition may be integrated in the ventral LPC. In line with this view, Goldberg and colleagues (2008) suggested that the inferior parietal lobule (ventral LPC) is able to generate behavior by using cues from the internal environment for making choices.

Taken together, the ventral LPC supports the planning and execution of internally driven actions by selecting the effectors of the action, as opposed to the dorsal LPC, which appears to support external aspects of planning, attentional control and movement regulation. Moreover, the role of the dorsal ACC in selecting external goals demarcates the mechanism by which apathy may be produced due to its dysfunction.

5.1.2. Movement intention and execution

The studies described in section 5.1.1 demonstrate that interaction of the LPC with other regions may enable different aspects of GDB. Another function that may result from similar interaction is the intention to act. Self-related processes are supported by midline structures in the cortex mediating the integration of processes evaluating reward potential in the subgenual ACC and medial prefrontal cortex, and autobiographical processes in the posterior cingulate cortex and precuneus (Northoff et al., 2006). Under certain circumstances, brain activation in the precuneus was found to predict the action to be performed, and occurred considerably before subjects reported awareness of their intention to perform a specific act. Increased activity in this region occurred several seconds prior to the motor response (Soon et al., 2008) and prior to subjects reported becoming aware of the choice (Soon et al., 2013). Moreover, the reported awareness of the movement intention paralleled increased activity in the angular gyrus of the ventral LPC. It may be possible that the posterior cingulate cortex/precuneus evaluates the self-relevance of an action and the ventral LPC is active after a future desired state (goal) is affirmed, triggering planning and performance of actions. In a broader context, connectivity between these regions enables integration of self-related processes with performed, imagined, and observed actions (Buckner and Carroll, 2007; Farrer et al., 2008; Lou et al., 2004).

5.2. A neurocognitive framework for GDB

In the studies described in section 4, we summarized cognitive processes involved in GDB including those occurring outside the LPC. These findings can be integrated to provide a neurocognitive framework of GDB (Fig. 3). In this framework, internal stimuli for intentional actions are produced in the posterior DMN and activate the LPC for forming an action plan. The ventral LPC in coordination with the dorsolateral prefrontal cortex evaluate multiple action plans with the former selecting the plan of choice and the body movements needed (Beudel and de Jong, 2009), and the latter is activated during rule-learning, external goal representations, and monitoring performance (Ridderinkhof et al., 2004). The dorsal LPC along with the dorsal ACC monitor external choices with the latter selecting the targets, and the former regulating action execution (Beudel and de Jong, 2009) as well as monitoring external outcomes (Botvinick et al., 2004). Execution of the necessary movement is regulated by control of attention and movement by the superior parietal lobule and intraparietal sulcus. The subsequent perception of the action performed and resulting changes in the external environment as caused by oneself (sense of agency) is mediated by the inferior parietal lobule (Chambon et al., 2015; Zwosta et al., 2015), whereas the medial prefrontal cortex evaluates the reward value of the outcome (Liu et al., 2011). Thus, the integration of segregated processes in the anterior and posterior as well medial and lateral cortical

regions represent the transformation of self-related processes of goal formation and intention to directed motor movements.

It is important to note that the flow of information between these regions occurs in a parallel fashion and not sequentially, where activity in each region biases activity in all other regions (Cisek and Kalaska, 2010). In addition, we have focused on the role of cortical networks in GDB, without considering the contribution of basal ganglia and thalamus to GDB. The reason for this is that distinct networks of sub-regions in these latter regions have not been defined consistently and their functions are unclear, although deficits in subcortical structures are associated with relatively greater degree of apathy compared to those with primarily cortical deficits (Stuss et al., 2000).

6. Revised model of apathy – role of LPC

Understanding the neural basis of apathy rests on models of GDB, the deficits of which have been suggested to produce negative symptoms such as apathy in neurological and psychiatric patients (Brown and Pluck, 2000). These symptoms were broadly classified into cognitive, motor, and affective subtypes based on deficits in specific neural substrates in the cortico-striato-thalamic circuits. To explain the cognitive processes affected in negative symptoms, a model of interconnected cognitive processes that produce GDB was proposed. The processes described in this model include intention, planning, initiation and execution of actions, and casual knowledge of a link between action and outcome. Subsequent models of apathy expanded upon this framework identifying deficits in the prefrontal cortex - basal ganglia circuits to underlie apathy (Levy and Dubois, 2006; van Reekum et al., 2005). Diagnostic criteria for apathy have been proposed, classifying apathy into three domains – behavioral, cognitive, and emotional (Robert et al., 2009). Our description above shows that critical aspects of GDB are supported by the LPC. These aspects like intention, initiation, and causal knowledge of action were included in previous models of GDB but these functions were not attributed to any brain region/network. We have shown the mechanisms by which these functions are supported by the LPC and proposed a revised model that describes the neurocognitive mechanisms of GDB incorporating the role of the LPC.

As reviewed in the preceding sections, the LPC supports the cognitive aspects of movement generation. Based on functions localized in the LPC, apathy may emerge through the following mechanisms. 1) Deficits in the dorsal LPC may reduce the ability to sustain attention for forming action plans and update ongoing actions according to the obtained feedback, which together may increase the effort required for generating behavior directed towards a goal. 2) Deficits in the ventral LPC likely perturbs internally generated action. The likely mechanism for this maybe disturbance in selecting an effector for action during planning and execution. In addition, disturbances in mapping

the proprioceptive state of the body, including the predicted sensory effects of movement, may also reduce the subjective feeling of intention and sense of agency or causal knowledge that results from executing intended actions.

The proposed neurocognitive framework presented in figure 3 incorporates the cognitive processes supported by the LPC, and figure 4 further describes the two mechanisms that are localized to the dorsal and ventral LPC. In contrast to lesion studies where a large part of a single region is typically affected, apathy is not likely to result from deficits in a single region as the disorders with symptoms of reduced behavior are not localized (with the exception of stroke). In these disorders, brain changes occur slowly and are diffuse in nature. Such changes may give rise to compensatory processes. Another consideration is that loss of function in one region affects other interconnected regions, as a result of which a deficit in the ventral LPC can be expected to produce changes in the DMN, FPCN, and salience network. Keeping these concerns in mind, behavioral consequences of deficits in the dorsal LPC are likely to be increased errors when performing actions. To compensate for errors, slowing of actions may occur. Deficits in the ventral LPC are likely to be associated with difficulty in initiating actions, but once initiated, further processes are performed without difficulty or errors. Thus, slowness of responses leading to increased reaction times may be common to both mechanisms.

As the model is based on the findings from cognitive experiments, the results and inferences are biased by the context in which GDB was assessed. These functions are typically assessed over relatively short durations and instructions for the expected actions are given to the participants, thus rendering experimental conditions not completely voluntary or self-paced. In comparison, patients with apathy show reduced self-generated behavior that occur over longer periods.

Between the two mechanisms, the ventral LPC (or inferior parietal lobule) region is more commonly reported to be affected in studies in apathy patients (section 2). Given its role of linking internally- and externally-directed cognitive functions supporting goal-directed actions, the ventral LPC forms a critical node in sensorimotor transformation. Moreover, this region has been shown to compensate for deficits in dorsal LPC function (Verhagen et al., 2013) but not vice- versa. Therefore, the ventral LPC and its associated functions of internally-driven selection of effectors of movement, its initiation, and attribution to oneself are more likely to be the deficient mechanisms in apathy. In-depth studies of apathy patients with cognitive tests are needed to evaluate the proposed mechanisms.

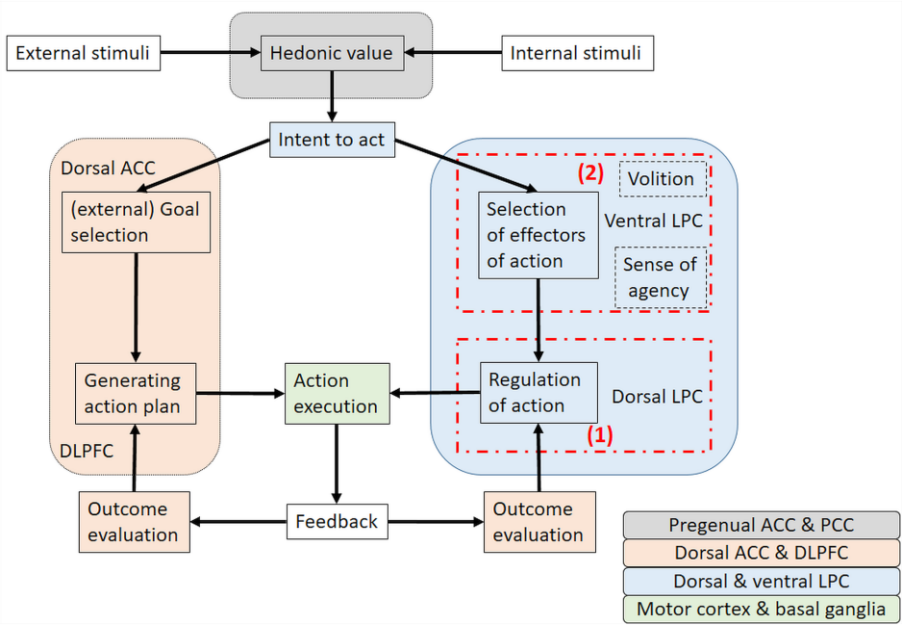


Fig. 3. Schematic framework of goal-directed behavior

The figure integrates various functions necessary for goal-directed behavior (GDB) and identifies likely brain regions that support these functions. This framework ascribes cognitive control of internally-directed motor behavior to regions of the lateral parietal cortex, and GDB consists of the following steps. External and internal stimuli are assigned a reward value by the pregenual anterior cingulate cortex. Based on the reward value, an intention to act (volition) is generated by interactions between the ventral LPC (internal parietal lobule) and the posterior cingulate cortex. The intent to act triggers preparation to generate actions. Externally-oriented processing in the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex assess various alternative paths to the goal and select an appropriate option. In parallel, internally-directed processing contributes to the selection and initiation of the appropriate external goal based on the body schema and achievable motor plans. The selected movement is operationalized in the dorsal LPC, which regulates fine control of the selected movement and necessary adjustments during its execution. Based on the visual feedback and changes in body schema, the ventral LPC evaluates the actual outcome with the predicted outcome. This evaluation contributes to the recognition of the agent of the action, i.e., whether the observed change was caused by the action performed (sense of agency). This process is facilitated by the ventral LPC. Simultaneously, the dorsal anterior cingulate compares the obtained result with the original goal.

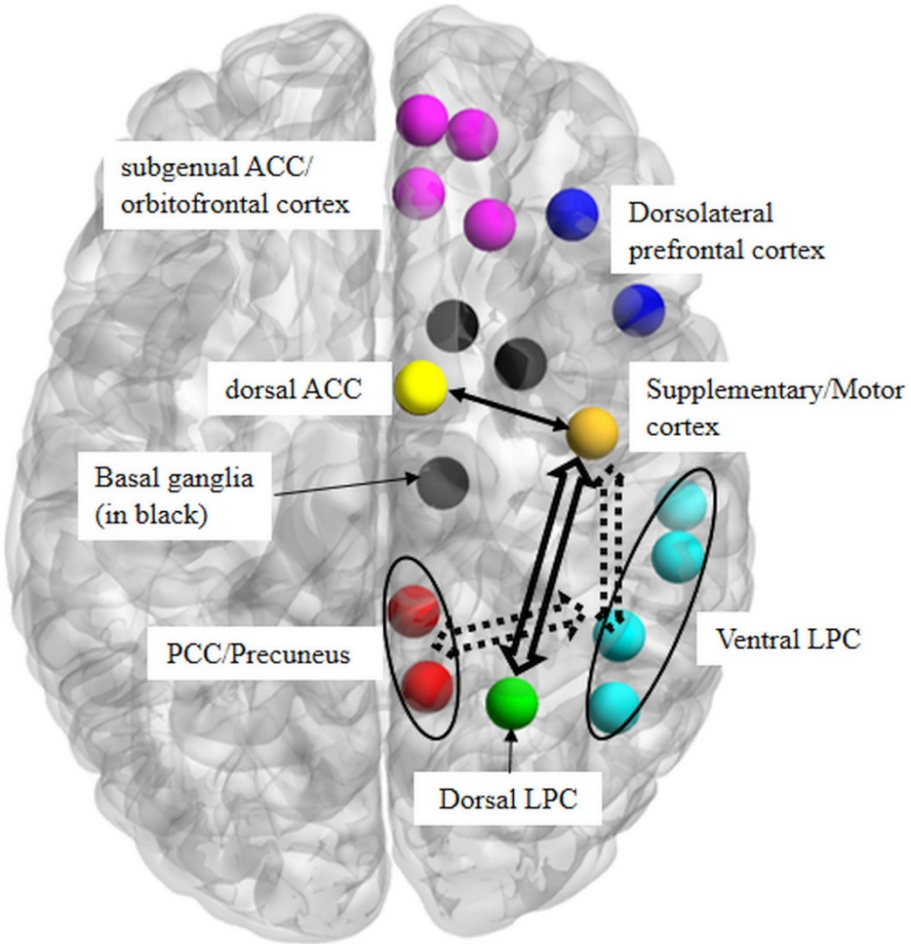


Fig 4. Brain regions involved in goal-directed behavior, focusing on the mechanisms of intention, and internally- and externally-directed decision-making

The regions of interest (ROI) are color-coded into groups that show largely similar functions. Thus, ROI in magenta indicate the pregenual anterior cingulate cortex and orbitofrontal cortex, which are involved in reward evaluation. ROI in dark blue indicate the lateral prefrontal cortex, which is involved in rule learning and framing of alterative goals. ROI in red indicate the posterior cingulate cortex and are associated with autobiographical processing. ROI in black indicate subcortical regions, whereas those in ochre indicate the primary and supplementary motor cortex, which together control the production of movements. ROI in yellow indicate the dorsal ACC. ROI in light blue

indicate those in the dorsal LPC while those in green indicate the ventral LPC. The arrows in the figure indicate the pathways through which motor behavior is regulated by the dorsal ACC and the parietal cortex. The thick black line indicates that the dorsal LPC regulates planning and rapid adjustment of movements. The dashed arrows from the ventral LPC to the posterior cingulate cortex and supplementary motor cortex indicates the interaction between these regions produces intention and sense of agency, respectively. The thin arrow between the dorsal ACC and supplementary motor cortex indicates inhibitory control over motor behavior.

7. Clinical implications for apathy

In the preceding sections we described a neurocognitive model to account for the associations between symptoms of apathy and the lateral parietal lobe in different brain disorders. The two parts of this model draw together the rich and independent literature on cognitive functions and large-scale networks that involve the LPC. Based on the several cognitive functions anchored in this region and necessary for performing motor behavior, the symptoms resulting from dysfunction in these regions may vary.

In clinical settings, apathy is assessed using various instruments. The most commonly used instruments include the AES (Clarke et al., 2007), Lille apathy rating scale (LARS) (Sockeel et al., 2006), apathy scale (AS) (Starkstein et al., 1992), and AI (Robert et al., 2002). Other commonly used instruments that assess multiple behavioral symptoms include the neuropsychiatric inventory (NPI) (Cummings et al., 1994), frontal systems behavioral scale (FrSBe) (Grace et al., 1999), unified Parkinson's disease rating scale (UPDRS) (Goetz et al., 2008) and positive and negative syndrome scale (PANSS) (Kay et al., 1987). In each of these scales, specific items assess symptoms that may result from impaired processes in the LPC. Such items may be broadly divided into those where patients need to be told what to do, and those requiring sustained control of complex motor movements. Examples of the former are: Is getting started by oneself important to the patient (AES), Lacks initiative (FrSBE, AES, LARS, AI), Puts little effort into anything (AES), Lack of spontaneity (PANSS), Less likely to initiate a conversation (NPI). Examples of the latter are: Mixes up sequences (FrSBe), Does not finish things (AI, AES, FrSBe), Does things with reminders (FrSBe), Do you try out new products or tools (LARS), Learning new things (AES), Doesn't care about doing new things (NPI).

The ventral LPC route to apathy will likely lead to symptoms where subjects experience difficulty in initiating actions, or selecting actions or linking the actions to outcomes, a difficulty which is solved when the choice of action need not be made. The dorsal LPC route to apathy can be expected to produce symptoms where deficits in

sustained control of complex motor movements impair the ability to learn new tasks, or engage in novel behavior. They can also lead to an inability to complete tasks, requiring repeated prompts to complete a task. Here routine activities and hobbies may be preserved. The contrast between the two symptom clusters – relative preservation of routine activities in dorsal-predominant LPC deficits and difficulty in initiating behavior but ability to complete tasks once initiated, distinguish the two routes. Together, the two categories of symptoms can be explained with the proposed mechanisms of apathy.

The presence of sub-types in apathy has been repeatedly suggested (Brown and Pluck, 2000; Levy and Dubois, 2006; Marin, 1990; Starkstein and Leentjens, 2008; Stuss et al., 2000; van Reekum et al., 2005). However, the questionnaires used to assess apathy do not identify these sub-types, or only attempt to do so in a limited way. The AES and the NPI are most commonly used but do not categorize symptoms into sub-types of apathy. The AI aims to identify the three standard sub-types but the symptoms for this classification are assessed with a limited number (2-3) of questions (Robert et al., 2002). The LARS uses a more extensive questionnaire, compared to the AES and AI, consisting of 33 items in 9 domains and yields scores for four categories – intellectual curiosity, emotion, action initiation, and self-awareness (Sockeel et al., 2006). It has been mainly used to characterize apathy in patients with Parkinson's disease, and to our knowledge, the neural correlates of each category have not been reported. Recent studies have advocated that dimensional scales be used in assessing apathy in amytrophic lateral sclerosis and traumatic brain injury patients as well (Arnould et al., 2013; Radakovic and Abrahams, 2014). One such instrument proposed is the Dimensional Apathy Scale, which is designed to assess three subtypes of apathy – cognitive/behavioral initiation, emotional, and executive variants (Radakovic and Abrahams, 2014). Similar approaches (e.g., Aleman, 2014) may provide insights into reduced behavior and help to identify associated neural deficits. Current approaches for assessing apathy are based on identifying or aggregating symptom clusters. Further research is needed to validate the neurocognitive mechanisms of subtypes of apathy, which calls for detailed symptom assessment and neuropsychological testing.

8. Conclusion

To summarize, we evaluated the association between apathy and the LPC in the extant literature and provided an analysis of the underlying neurocognitive mechanisms. A review of studies in patients and in healthy subjects provided evidence for the role of the LPC in supporting the cognitive aspects of action generation. Within the LPC, contributions of the dorsal and ventral subdivision appear to be relatively more important for control of external action planning and regulation, and internal planning, intentionality, and monitoring internal feedback, respectively. These cognitive deficits

are suggested to give rise to distinct behavioral features such as difficulty in learning new tasks or the need for prompts to complete an initiated task in case of dorsal LPC impairment, and difficulty in initiating actions and reduced engagement in routine or habitual actions in case of ventral LPC impairments. In both cases, patients are expected to take more time to perform tasks. We also described the framework of GDB after incorporating the LPC, attributing specific functions of GDB to it.

In conclusion, we propose that deficits in neural processes occurring in the LPC may contribute to the development of symptoms of apathy. These involve (i) deficits in the control of intentional movements in the dorsal LPC, specifically aimed at new external circumstances, and (ii) deficits in internally driven actions supported by the ventral LPC, associated with a general difficulty in selecting a specific action outflow channel. Such deficits may explain the reports of LPC associations with apathy across various disorders and deserve to be studied in more detail.